UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,057	02/03/2004	Gregory E. Conner	GEC-001-2US	1518

7590 07/17/2008

Gregory E. Conner
Department of Cell Biology and Anatomy; R-124
University of Miami School of Medicine
P.O. Box 016960
Miami, FL 33101

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
07/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,057	CONNER, GREGORY E.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-11,18,19 and 21-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-11, 18-19, 21-28* is/are rejected.

7)☒ Claim(s) *26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 4-11, 18-19, and 21-28 are pending. Applicants cancelled claims 3, 12-17, and 20. Applicants have amended claims 2, 4-9, 11, and 18. Claims 21-28 are new. Applicants amended claim set and remarks/arguments submitted on 10/12/2007 are acknowledged. All rejections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments.

Claim Objections

Claim 26 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 26 fails to further limit parent claim 10, because parent claim 10 is drawn to treating a lung infection by administration of hydrogen peroxide; a lung infection once manifested cannot be prevented; and decreasing progression of said lung infection reads on treating a lung infection. For these reasons, it is concluded that claim 26 fails to further limit parent claim 10.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-11, 18, and 21-26 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicants' claims are broad with regards to the amount and concentration of hydrogen peroxide administered to the respiratory system of a mammal (clam 10 and claims dependent therefrom) or a primate (claims 1 and 11 and claims dependent therefrom). Applicants' independent method claims are broad with regards to the condition being treated in a patient exhibiting symptoms of cystic fibrosis (claim 1) or the lung infection being treated (claim 10),

and thus include all lung conditions possible in patients with cystic fibrosis as well as any kind of infection (i.e. viral, fungal, bacterial, or parasitic).

Nature of the invention/State of the Prior Art

Applicants' invention is drawn to methods of treating lung conditions and/or lung infections in mammals, especially primates, exhibiting symptoms of cystic fibrosis, by administration of hydrogen peroxide optionally in combination with antifungal and antiviral agents. Some of Applicants embodiments require the coadministration of thiocyanate. Thiocyanate is an anion, thus, the recitation of thiocyanate in Applicants' claims is considered generic to any thiocyanate salt, because anions cannot stably exist in the absence of a suitable cationic counterion to yield a charge neutral ionic compound. Applicants' claims require no specific amount of hydrogen peroxide or thiocyanate anion. It is noted that instant claims 9 and 18 only require a specific concentration of hydrogen peroxide as one of two possible alternative limitations.

An online Material Safety Data Sheet (MSDS-1) (accessed on July 10, 2008 at http://www.bu.edu/es/labsafety/ESMSDSs/MSHydPeroxide.html) teaches that 30% w/w hydrogen peroxide (aq) is harmful when inhaled, causing chemical burns to the respiratory tract; may cause irritation to the respiratory tract with burning pain to the nose and throat, coughing, wheezing, and shortness of breath. The MSDS also teaches that inhalation of 30% hydrogen peroxide may also cause ulceration of nasal tissue, insomnia, nervous tremors with numb extremities, chemical pneumonia, **unconsciousness, and *death***. The MSDS (MSDS-2) (accessed on July 10, 2008 at http://www.jtbaker/msds/englishhtml/h4070.htm) for 3% aqueous

hydrogen peroxide solution teaches that inhalation of a 3% aqueous hydrogen peroxide solution is not expected to be a health hazard under normal conditions and that inhalation of a 3% aqueous hydrogen peroxide solution is not expected to require first aid measures. MSDS-2 does not specify what are "normal conditions" nor under what circumstances first aid measures might be required upon inhalation of a 3 % aqueous hydrogen peroxide solution. The medical literature has recognized some cases of serious side effects or even fatal poisoning resulting from the non-accidental or accidental ingestion of 3% aqueous hydrogen peroxide (Ashdown et al. "Hydrogen Peroxide Poisoning: Causing Brain Infarction: Neuroimaging Findings," A.J.R. June 1998, 170, pp 1653-1655, especially pg. 1655, 1st sentence of discussion section). Watt et al. ("Hydrogen peroxide poisoning," Toxicol. Rev. 2004, 23(1), Abstract only) teach that almost most inhalational exposure [to hydrogen peroxide] causes little more than coughing and transient dyspnea (i.e. difficult or painful breathing), but highly concentrated solutions of hydrogen peroxide can cause severe irritation and inflammation. Shock, coma, and convulsions may ensue and pulmonary edema may occur up to 24-72 hours post exposure (ibid). See also an online excerpt from "International Programme on Chemical Safety Poisons Information Monograph 946: Chemical", sections 2.2, 5.2, and 9.1.2 (accessed July 11, 2008 at http://www.inchem.org/documents/pims/chemical/pim946.htm).

The MSDS (MSDS-3) (accessed on July 10, 2008 at http://www.jtbaker/msds/englishhtml/p6181.htm) teaches that **inhalation of potassium thiocyanate causes irritation to the respiratory tract**, with symptoms including coughing and shortness of breath. The probable lethal dose of potassium thiocyanate is 15-30 grams.

Regarding infections, it is not logical that one can prevent an infection that is already present, such as Applicant claims in alternative limitations recited in claims 23 and 26. The art recognizes that the lactoperoxidase system (LPO system), which is based on the conversion of hydrogen peroxide and thiocyanate by a lactoperoxidase into the antibiotic $OSCN^-$ anion is effective against *Pseudomonas* (various species), *Staphylococcus aureus, Escherichia coli, Streptococcus* (various species), *H. influenzae, Bacillus cereus, and B. cepacia* [(1) Wijkstrom-Frei et al. "Lactoperoxidase and Human Airway Host Defense," Am. J. Respir. Cell Mol. Biol. 2003, 29, pp 206-212, especially pp 210-211; and (2) Conner et al. "The Lactoperoxidase system links anion transport to host defense in cystic fibrosis," FEBS letters 2007, 581, pp 271-278, especially pg. 272]. The art also recognizes that the LPO system is present in ovine and human airways [(1) Wijkstrom-Frei, ibid, abstract and (2) Conner et al., ibid, pp 271]. Conner et al. acknowledges that continuous production of hydrogen peroxide and transport of thiocyanate (i.e. SCN^-) in the presence of LPO in vivo may not be able to eradicate an established infection (pp 276, right column, 1st full paragraph). Conner's data in Figure 3 on pg. 274 indicates that **addition of LPO or hydrogen peroxide in the absence of added SCN^- to washes from cultured secretions from cystic fibrosis (CF) lungs was unable to restore antibacterial activity in CF cultures** and only non-CF cultures showed antibacterial activity upon addition of LPO or hydrogen peroxide. Conner speculates that defects in SCN^- transport in cystic fibrosis (CF) patients may be an additional defect in the CF airway host defense and supports the need for further studies of SCN^- levels in CF airways (pp 277, last two sentences prior to the acknowledgements). Wijkstrom-Frei teaches that **the efficacy of the LPO antibacterial activity is known to depend on concentration of hydrogen peroxide, thiocyanate, and bacteria** (pg.

210, left column). Wijkstrom-Frei states that **the exact concentration of hydrogen peroxide in airway surface liquid (i.e. in the lung fluid) is unknown and is estimated to range from 10^{-6} to 10^{-4} M** (pp 211, 1st full paragraph in left column).

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970).

Guidance/Working Examples

Applicant's specification provides no guidance about what specific concentration of hydrogen peroxide is effective, but merely states that the amount administered results in a lung fluid concentration between 10^{-7} M and 10^{-4} M (see page 5, lines 4-7 of Applicant's specification). Similarly, Applicant's specification provides no guidance with regards to the amount of thiocyanate when administered is effective to treat a lung condition in primates exhibiting signs of cystic fibrosis or to treat lung infections in a mammal, but merely states that the amount administered results in a lung fluid concentration between about 5 micromolar and 4 mM (see page 4, lines 10-15 of Applicant's specification). Thus, an ordinary skilled artisan would be forced to rely on undue experimentation to discover the therapeutically effective ranges in the amounts and concentrations of both hydrogen peroxide and thiocyanate (e.g. potassium thiocyanate).

In conclusion, Applicant's specification is not enabling for the use of the claimed methods of treatment, as set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 18, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, 18, and 27 are vague and indefinite, because each of these claims recites an alternative limitation requiring the administration of hydrogen peroxide "in an amount between 10^{-7} M and 10^{-4} M in the lung fluid" Molarity (i.e. M) is a unit of measurement indicating a concentration. Concentrations are not indicative of an amount. Thus, it is unclear how much hydrogen peroxide is administered. Appropriate correction and clarification are required.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 19 and 27-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Lin et al. (U.S. Patent No. 6,589,481).

Applicants claim an inhaler comprising (a) hydrogen peroxide, (b) a peroxidase, or (c) thiocyanate (claim 19), which (i) administers an amount of hydrogen peroxide to the respiratory

system of a mammal to decrease microbial load, (ii) administers hydrogen peroxide in an amount between 10-7 M and 10-4 M in the lung fluid, or (iii) further comprises an antibiotic, an anti-fungal, or an anti-viral (claim 27), or which comprises (a) hydrogen peroxide, (b) a peroxidase, or (c) thiocyanate and hydrogen peroxide (claim 28).

Lin teaches an apparatus to pretreat and sterilize a lumen device, which in some embodiments **the generator of the mist or aerosol comprises a liquid spray nozzle, a tank containing a liquid comprising hydrogen peroxide with a gas nozzle situated at least partially in** the liquid or **a nebulizer** (col. 3, lines 3-6). A nebulizer reads on an inhaler. The minimal requirement of Applicants' rejected claims is an inhaler comprising hydrogen peroxide, because items (a), (b), and (c) in claims 19 and 27-28 or all written in the alternative. The intended use of items (a) and (b) of claim 27 is given little patentable weight. Furthermore, claims 19 ands 27-28 do not specify the amount of hydrogen peroxide contained in the inhaler nor its concentration. Thus, any amount of hydrogen peroxide that could be administered from the inhaler must be reasonably expected to decrease microbial load if administered to the respiratory system of a mammal.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 4-11, 18, and 21-26 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,702,998 (USPN '998) for the reasons of record restated herein. **New claims 21-26 are appended to this rejection** for the reasons of record.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are substantially overlapping in scope and mutually obvious. Independent claims 1 and 10 of the instant application, claim methods of treating a lung condition (claim 1) or a lung infection (claim 10) in a primate exhibiting signs of cystic fibrosis (claim 1) or a lung infection in a mammal (claim 10) by administering an effective amount of hydrogen peroxide. Independent claims 1 and 10 of USPN '998 claim a method of treating a lung infection in a primate suffering from cystic fibrosis (claim 1) or a mammal (claim 10) by administration of aerosolized thiocyanate. Dependent claims 5 and 15 of USPN '998 indicate that hydrogen peroxide can be also be administered with the aerosolized thiocyanate in the methods of independent claims 1 and 10. Both USPN '998 and the instant application recite methods of treating lung infections (i.e. lung conditions) in primates (i.e. mammals) suffering from cystic fibrosis comprising administration of thiocyanate, a peroxidase, and/or hydrogen

peroxide. The specific infective bacteria listed in claim 21 of the instant application are also recited in claims 3 and 12 of USPN '998. Both the instant application and USPN '998 also recite the combination of other treatments including breathing exercises, postural drainage, chest percussion, vibration, or assisted coughing. Importantly, claims 5 and 14 of USPN '998 claim a method of treating a lung infection in a primate suffering from cystic fibrosis (claim 5) or treating a lung infection in a mammal (claim 14) that further comprises in one alternative the step of administering hydrogen peroxide. The difference between the cited independent claims of the instant application and USPN '998 is that the claims of the instant application administer hydrogen peroxide and the claims of USPN '998 administer thiocyanate. It is noted that several of Applicant's claims suggest in alternative limitations the administration of other active agents (e.g. thiocyanate). Thus, as evidenced by claims 5 and 14 of USPN '998, the administration of hydrogen peroxide to treat a lung infection, which is a species of lung condition, in primates exhibiting symptoms of cystic fibrosis or mammals having a lung infection represents an obvious modification of the claims of USPN '998. Therefore the Examiner concludes that claims 1-2, 4-11, 18, and 21-26 are prima facie obvious variants of claims 1-17 of USPN '998.

Response to Arguments

Applicant did not traverse the instant rejection and has proposed filing a terminal disclaimer at a later date upon indication of allowable subject matter. The instant rejection is maintained.

Conclusion

Claim 26 is objected. Claims 1-2, 4-11, 18-19, and 21-28 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.H.A.-A.
Patent Examiner
Technology Center 1600

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616